Order Code RS21418
Updated March 8, 2005

Regulation of Plant-Based Pharmaceuticals

Geoffrey S. Becker
Resources, Science, and Industry Division
Donna Vogt
Domestic Social Policy Division

Summary

Among many genetically engineered crops being developed are a number modified to produce pharmaceutical compounds (none yet commercialized). Proponents say such plant-based proteins could be produced more cheaply than by conventional methods and economically benefit farmers. But critics see risks, such as potential environmental, food safety, and trade problems. Among the issues is whether the current system for regulating biotechnology is adequate. This report will be updated if events warrant.

Introduction[1]

Since the first genetically engineered (GE) crop varieties became commercially available in the mid-1990s, U.S. farmers have been rapidly adopting them in efforts to lower production costs and raise crop yields. Among many new GE crops now in development, but not yet commercialized, are plants that could be "factories" for pharmaceutical compounds, which could be extracted and purified for specific human and animal health uses. Worldwide, hundreds of GE, plant-based pharmaceuticals are being developed. Proponents believe they could produce proteins that might, for example, be used to vaccinate against and/or treat various forms of cancer, infectious diseases, nervous system and cardiovascular diseases, metabolic disorders, and agents of biowarfare. A number of applications could be approved within 10 years, according to some experts.

In the United States in 2004, seven companies and universities had USDA permits to field test pharmaceutical production in the following crops: corn (3 permits); tobacco, or tobacco mosaic virus (TMV) using tobacco as the host (3); and safflower (1). Test plot locations for these crops were approved for Florida, Arizona, Nebraska, Kentucky, Missouri, South Carolina, Texas, and Colorado.[2]

---

[1] This section's sources include the Biotechnology Industry Organization, Pew Initiative on Food and Biotechnology, and CRS Issue Brief IB10131, *Agricultural Biotechnology: Overview and Selected Issues*. Contacts: Tadlock Cowan (7-7600) on agricultural and USDA aspects of this report; Donna Vogt (7-7285) on medical, food safety, and Food and Drug Administration aspects.

[2] Personal communication with Legislative and Public Affairs Office, USDA's Animal and Plant
(continued...)

Potential Benefits. Proponents contend that plant-based pharmaceuticals could be a far cheaper alternative — as low as pennies per dose compared with many dollars to produce those now made by more conventional methods. These conventional methods require major investments in both large volumes of purified culture mediums and in manufacturing plants. Plant-based pharmaceuticals, on the other hand, are highly cost-efficient protein producers, which could be easily incorporated into the existing agricultural infrastructure and by well-managed farms, proponents argue. Many thousands of acres could be converted to "pharming" for higher earnings. Corn farmers, for example, might gross thousands of dollars per acre for pharmaceutical varieties compared with several hundred dollars for the feed corn they grow now, advocates argue, noting that there has been support from some major corn growing regions for this technology. Many experts consider pharmaceuticals from plants to be safer than those from mammalian sources, as small amounts of pathogenic material from a host animal could mix with and contaminate the new compound. No known plant viruses have infected humans, unlike animal pathogens.

Potential Risks. Corn is the crop most extensively used and researched for GE uses, including pharmaceuticals. Corn also is the most widely planted U.S. crop at approximately 80 million acres annually, most of it destined for animal feed (and indirectly meat and poultry), and corn meal, oil and syrup used in many processed foods. Some critics want "pharmed" corn to be banned from areas where food and feed corn are produced. Critics worry that corn's open pollination makes it difficult to prevent pollen drift and gene flow into other corn varieties, and are concerned about impacts for food crops and wildlife. Also, some major foreign buyers already are reluctant to accept any U.S. crops for which GE varieties are used — despite U.S. assertions that approved GE crops (all of them non-"pharm") are no different than, and as safe to consume as, those produced by more traditional means. Keeping GE "pharmed" corn separate from food and feed implies higher production costs. Large scale production of "pharmed" corn also might bring more foreign opposition to products of agricultural biotechnology.

Regulation

The basic federal guidance for regulating all biotechnology products, including plant-based pharmaceuticals, is the **Coordinated Framework for Regulation of Biotechnology** (51 *Fed. Reg.* 23302) published in 1986 by the White House Office of Science and Technology Policy (OSTP). A key principle is that genetically engineered products should continue to be regulated according to their characteristics and unique features, and not according to their production method. The Framework provides a regulatory approach intended to ensure the safety of biotechnology research and products, using existing statutory authority and previous agency experience with traditional breeding techniques.

---

[2] (...continued)
Health Inspection Service (APHIS), March 7, 2005. In 2002, more than 15 companies and universities had USDA permits to field test pharmaceutical production in the following crops: corn (41 permits); tobacco, or tobacco mosaic virus (TMV) using tobacco as the host (18); rice (8); and alfalfa, barley, rapeseed, sugarcane, and tomato (1 each), according to USDA/APHIS data compiled by Information Systems for Biotechnology at Virginia Tech ([http://www.isb.vt.edu/]).

The three lead agencies are USDA's **Animal and Plant Health Inspection Service (APHIS)**, which regulates the importation, interstate movement, and field testing of GE plants and organisms that are or might be plant pests under the Plant Protection Act (PPA; 7 U.S.C. §7701 *et seq.*) and which regulates animal biologics (i.e., viruses, serums, toxins for animal vaccines) under the Virus, Serum, and Toxins Act (21 U.S.C. 151 *et seq.)*; the **Food and Drug Administration (FDA)**, which regulates food, animal feed additives, human and animal drugs and medical devices, including those from biotechnology, primarily to ensure that they are effective and pose no human health risks, mainly under the Federal Food, Drug and Cosmetic Act (FFDCA; 21 U.S.C. §301 *et seq.*) and the Public Health Service Act (42 U.S.C. §201 *et seq.*); and the **Environmental Protection Agency (EPA)**, which must approve the use of all pesticides, including those genetically engineered into plants. Developers of plant-based pharmaceuticals mainly work with APHIS and FDA, often at the same time; both agencies share information about a product during its development and testing. Such products also may be subject to state laws.[3]

APHIS.[4] GE plants that are or might be plant pests are considered "regulated articles" under APHIS regulations (7 CFR 340-340.9). APHIS authorization must be obtained prior to import, interstate movement, or environmental release, including field testing. To gain "non-regulated status" (so that a plant can be freely commercialized with no further oversight), a developer must provide APHIS with extensive information on plant biology and genetics, and potential environmental and plant pest impacts that may result from the modification. APHIS conducts a formal environmental assessment (EA) and has public comment periods before deciding whether to approve the petition. It is only after years of field testing, scientific review of extensive data, and a public comment period that "non-regulated status" may be granted. Until then, a "regulated" plant cannot be introduced into the environment, even field tested, unless its developer obtains authorization through either the (1) notification or (2) permit process. Sponsors follow APHIS guidance on testing and movements to ensure that the plant will not damage agriculture, human health, or the environment. "Pharm" plant developers must utilize the permit, not the notification, process.

Notification. The majority of GE crops are developed under the notification option, a less rigorous process than permitting. Developers must obtain authorization from APHIS before interstate movement, import, or field testing of a GE organism. APHIS then either authorizes or denies the notification, within 10 days for interstate movement, and 30 days for a field test notification. Authorization is valid for one year, with renewals through additional notifications. The developer must submit a report within six months after completion of field tests and also inform APHIS of any unusual occurrence during tests. Under the notification process, the agency generally inspects about 10% of current

---

[3] *CEQ and OSTP Assessment: Case Studies of Environmental Regulations for Biotechnology* (January 2001), by the White House Council on Environmental Quality, provides a more detailed look at how the federal regulatory system for biotechnology functions, applying it to specific products, including a plant-based pharmaceutical (see [http://www.ostp.gov/html/012201.html]).

[4] Sources include CRS Report RL30198, *Food Biotechnology in the United States: Science, Regulation, and Issues*; the Pew Initiative's *Guide to U.S. Regulation of Genetically Modified Food and Agricultural Biotechnology Products*; BIO's *Reference Document for Confinement and Development of Plant-Made Pharmaceuticals in the United States*; Belson, Neil A., "U.S. Regulation of Agricultural Biotechnology: An Overview," in *AgBioForum*; and various APHIS materials summarizing confinement and related measures for plant pharmaceutical field tests (APHIS website: [http://www.aphis.usda.gov/brs/]).

trials annually. Once "non-regulated," a crop can go into commercial use and is no longer subject to confinement measures and other APHIS oversight.

Permit. GE plants for pharmaceuticals fall into a distinct regulatory category handled differently by APHIS than GE plants for food or feed use. The permit process is much more stringent than notification, starting with application, which must be at least 120 days in advance of environmental release, and at least 60 days in advance for movement. Required permit information is more extensive than under notification, as is the subsequent list of permit conditions. An environmental analysis (EA) may have to be conducted under the National Environmental Policy Act (NEPA; 7 CFR 372 *et seq*.), with opportunity for public comment, prior to permitting. Generally, confined field trials do not require an EA if they fit certain categorical exclusions under NEPA (7 CFR 372.5), which APHIS has applied to virtually all recent plant-based "pharm" tests. However, an EA is required when the organism involves a new species, or the organism or a novel modification raises new issues.[5] Once APHIS initially agrees to a permit, a letter and proposed conditions go to the state, which can add its own conditions before approval, or even deny the permit. APHIS says it defers to the states on final decisions about permits.

APHIS specifies field test, movement and storage procedures to ensure that GE plants and seeds for pharmaceuticals do not enter the food and feed supply; requires a chain of custody and identity preservation system that tracks seeds from shipping through planting, harvest, and product extraction; and sets forth federal auditing requirements, among other rules. APHIS inspects all pharmaceutical field trials at least annually. APHIS materials (footnote 4) summarize in more detail the confinement measures for pharmaceutical organisms that were field tested in 2002. Examples of such measures, which are crop-specific, include geographically isolating test plots; planting buffer/border rows of non GE crops; preventing pollination or otherwise blocking reproduction; adequately identifying and segregating the organism; post harvest restrictions on test plots; destruction of leftover GE plant material; and a contingency plan to deal with any accidental releases. Developers are subject to civil or possibly criminal penalties for violating permit conditions.

Unlike plants engineered for use as food or feed which may be granted non-regulated status, no GE pharmaceutical plant has been declared "non-regulated" by APHIS. Agency officials told CRS that they cannot envision deregulating pharmaceutical plants — thus meaning that in commercialization they will be grown under both APHIS permit and FDA regulation (in the case of a plant-made veterinary biologic, also APHIS).

FDA. FDA currently regulates modified plant products as it regulates human and animal drugs and human biologic products. (FDA's rules are found in 21 CFR 201 *et seq*.; 301 *et seq*.; 501 *et seq*.; 601 *et seq*.). A "pharmed" ingredient intended for therapeutic use must meet the same quality standards of safety, purity, potency, and effectiveness as traditionally synthesized pharmaceuticals. Regardless of the production method, FDA regulations require manufacturers or sponsors to file New Drug Applications (NDAs), or Biologics License Applications (BLAs) which include all reports of clinical studies and information on the safety and supply of raw ingredients used to make the finished product. Also, the ingredients must be reproducible with consistent quality over an extended time.

---

[5] APHIS said it has strengthened its EA guidelines, including posting EAs for pharmaceutical and industrial crop field tests on its website and accepting public comments on them.

When a pharmaceutical company or sponsor already holds an approved application, and wants to substitute a plant-based pharmaceutical ingredient in the drug or biologic, it must file a supplemental application reconfirming the safety and efficacy of the final drug/biologic product. However, as the application is being reviewed and evaluated, the agency must reinspect the facility and production line where the new drug or biologic will be manufactured to ensure that it will be made to specification, and according to good manufacturing practices (GMPs). The entire manufacturing process, from seed banks, field preparation, planting, cultivating, harvesting, storage, transportation, extraction, to the purification of ingredients to be used in the finished product, must also comply with GMPs. The sponsor also needs to demonstrate that the pharmaceutical ingredient contains no allergens, anti-nutrients, toxic compounds, or heavy metals or other materials from the host plant that could adversely affect the safety or effectiveness of the pharmaceutical.

Under NEPA, FDA must consider the potential environmental impact of its decisions. Most drugs and biologics are eligible for exclusion from this rule because their ingredients are manufactured in enclosed facilities. Many plant-made pharmaceuticals likely would be field produced and not necessarily be excluded; however, it is likely that FDA would defer to APHIS for environmental reviews of pharmaceutical plants grown outdoors. FDA reviews for NEPA would probably focus on potential environmental impacts posed by uses after harvest that are not subject to APHIS oversight.

FDA is evaluating a number of regulatory options should plant-based GE pharmaceutical ingredients end up in the food supply. Should this happen, FDA might consider the food adulterated, and take some sort of administrative action. Some critics of current rules have suggested the agency approve plant-made pharmaceutical proteins as if they were food additives. In such instances, if trace amounts were found in food, the food would not be considered adulterated automatically, and there might not be need for a recall.[6] However, the food additive approval process is lengthy and costly. In addition, by establishing acceptable levels, the agency is stating that this material is safe for consumers, which may not be true. For these reasons, agency officials do not want to spend limited resources establishing acceptable levels when the pharmaceutical ingredients are not ordinarily found in food, an FDA official told CRS (personal communication, January 17, 2003). He added that because of consumer reaction, food manufacturers are unlikely to accept such material.

Regulatory Concerns and Issues

The ProdiGene Case. In 2002, material from GE-altered corn plants that had been test-planted in a prior growing season in Nebraska for pharmaceutical use (for ProdiGene, Inc.) was inadvertently mixed with some 500,000 bushels of soybeans, which had to be quarantined by USDA to keep them out of the food supply. In a December 6, 2002, press release, USDA announced that ProdiGene had agreed to pay a civil penalty of $250,000, to reimburse USDA for destroying the beans, post a $1 million bond, and meet higher field testing compliance standards. USDA officials observed that the soybeans never reached the food or feed supply, evidence that current regulatory oversight is effective. Critics countered that the ProdiGene case illustrates the dangers of growing plant-based drugs, and predicted a consumer backlash if government regulation is not

[6] In 2001, StarLink™ corn, a GE corn approved only for animal and not human food, was found in taco shells. CRS Report RS20732, *StarLink™ Corn Controversy: Background.*

strengthened. Proponents argue that careful management and oversight of test sites can address such concerns.

Nonetheless, concerns persist among both consumer groups and the food manufacturing industry about producing GE plant-made pharmaceuticals in food crops. These critics believe that any cross-contamination of the food supply could create a situation in which FDA would consider such foods "adulterated" under safe food law and subject to enforcement actions. Some food industry representatives want 100% prevention systems in place before the first product is commercialized. Some critics suggest that only non-food crops should be used for GE plant-made pharmaceuticals, or, at minimum, that GE food plants shed no pollen. Other potential issues include whether manufacturers of plant-based pharmaceuticals will be able to maintain consistency in dosages and overall quality; and unanticipated environmental problems (e.g., threatening endangered species).

Regulatory Modifications. Even before the ProdiGene incident, regulators were reassessing oversight procedures for GE crops in general and plant-based pharmaceuticals in particular. Also, APHIS published in the March 10, 2003, *Federal Register* a notice tightening permit conditions for any 2003 field tests of GE plants with pharmaceutical and industrial traits. The new changes include: (1) no traditional corn can be grown within one mile of pharmaceutical or industrial field test sites involving open-pollinated corn and within one-half mile of test sites for controlled pollinated corn (twice the prior distance rules), and border rows of nontransgenic corn no longer can be used to reduce these distances; (2) for all pharmaceutical crops (corn and other), fallow zones around test sites are doubled to 50 feet; (3) restrictions on what can be grown on a test site and fallow zone in the next growing season; (4) use of dedicated machinery (e.g., harvesters, planters) and storage facilities (for both the product and machinery) to be used only for pharmaceutical production — adequate cleaning for other uses is no longer acceptable; (5) equipment cleaning and seed cleaning and drying procedures must be submitted for APHIS approval; (6) an APHIS-approved staff and cooperator training program; (7) an increase in APHIS field site inspections from one per season, to five per season plus two visits the following year to look for any volunteer plants; (8) more recordkeeping requirements.

In the January 23, 2004, *Federal Register*, APHIS published a notice of its intent to prepare an environmental impact statement (EIS) evaluating its biotechnology regulations generally, and requesting public comment on a number of possible changes. These include whether to broaden APHIS's regulatory scope to cover GE plants that may pose a noxious weed risk or may be used as biological control agents; whether to establish new categories for field testing that delineate requirements based upon relative levels of potential risk; and whether to change (i.e., strengthen) its environmental reviews and permit conditions for GE plants producing pharmaceuticals and industrials. The agency received over 3,000 comments on its proposal. APHIS was expected to publish a draft EIS sometime in 2005.

Another focal point has been a draft document, published September 6, 2002, *Guidance for Industry: Drugs, Biologics, and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals* (available at [http://www.fda.gov/cber/gdlns/bioplant.pdf]). Prepared by FDA and USDA, it represents federal agencies' recent thinking on what kinds of information sponsors should develop and submit with requests for approvals of drugs and biologics made with plant-based pharmaceuticals.